Original Article

Malignancies in Patients with Inflammatory Bowel Disease: Results from 20 Years of Follow-up in the IBSEN Study

Øistein Hovde, a,b Marte Lie Høivik, b Magne Henriksen, d Inger Camilla Solberg, c Milada Cvancarova Småstuen, c Bjørn A. Moum b,c

aDepartment of Gastroenterology, Innlandet Hospital Trust, Gjøvik, Norway bInstitute of Clinical Medicine, University of Oslo, Oslo, Norway cDepartment of Gastroenterology, Oslo University Hospital, Oslo, Norway dDepartment of Gastroenterology, Østfold Hospital, Fredrikstad, Norway

Corresponding author: Øistein Hovde, MD, Department of Gastroenterology, Innlandet Hospital Trust, Kyrre Greppsgt. 19, 2819 Gjøvik, Norway. Tel.: +47 61157002; Fax: +47 61157439; email: oistein.hovde@sykehuset-innlandet.no

Abstract

Background and Aims: Whether patients with inflammatory bowel diseases [IBDs] have increased risk of developing cancer has been debated. The aims of the study were to determine the prevalence of intestinal/extraintestinal cancers in an IBD cohort 20 years after diagnosis and to assess whether these patients had an increased cancer-specific risk compared with a matched control population.

Methods: Patients with ulcerative colitis [UC] and Crohn’s disease [CD] diagnosed 1990–1993 have been prospectively followed up for 20 years. Follow-up visits were carried out 1, 5, 10, and 20 years after inclusion. Data on all cancer cases, deaths, and causes of death were collected from the Cancer Registry of Norway and from the Norwegian Cause of Death Registry.

Results: In all, 756 patients [519 UC and 237 CD] were diagnosed with IBD. Increased risk of cancer was seen in UC patients [hazard ratio [HR] = 1.40, 95% confidence interval [CI] 1.08–1.81, p < 0.01], but not in CD patients [HR = 1.23, 95% CI 0.80–2.03, p = 0.30]. Stratified by gender, our data revealed a statistically increased risk for all cancers only in male UC patients compared with the controls [HR = 1.51, 95% CI 1.08–2.11, p = 0.017]. In both groups breast cancer was seen more often than expected.

Conclusions: Male UC patients display an increased risk of development of colorectal cancer and, also all cancers combined, compared with the controls. In both UC and CD, standardized incidence ratio for breast cancer was increased.

Key Words: Inflammatory bowel diseases; malignancies

1. Introduction

Crohn’s disease [CD] and ulcerative colitis [UC] are chronic relapsing inflammatory diseases of the gastrointestinal tract collectively called inflammatory bowel disease [IBD]. The causes of the diseases remain unknown. Typically, IBD is diagnosed between the ages of 20 and 40 years and can cause a wide variety of clinical signs and symptoms.1–3 Involvement of extraintestinal organs, such as joints, skin, bile ducts, and eyes, is not uncommon. The highest reported prevalences of IBD are in Europe [827 per 100 000 inhabitants] and North America [578 per 100 000 inhabitants], and most time-trend analyses have shown a significantly increasing incidence, especially in infants and adolescents with CD. Robust epidemiological data from developing countries are lacking, but the incidence and prevalence are increasing throughout the world.4,5 Therefore, it is important to obtain reliable data on the different disease outcomes.
IBD-related cancers are those attributable to chronic inflammation and/or to medical treatment of the diseases, i.e. immunosuppressive drugs and/or biologics. Both intestinal and extraintestinal malignancies have been linked to IBD. However, few longitudinal, prospective studies have focused on the association between IBD and the development of malignancies.

The aims of the present study were first to determine the prevalence of intestinal and extraintestinal cancers in a well-defined, population-based cohort of IBD patients 20 years after diagnosis and, second, to assess whether the IBD patients were at an increased cancer-specific risk compared with age- and gender-matched individuals from the normal population.

2. Materials and Methods

The Inflammatory Bowel South-Eastern Norway [IBSEN] study prospectively followed all patients [n = 756] diagnosed with IBD from 1 January 1990, to 31 December 1993, in four geographically well-defined areas in south-eastern Norway. Each patient was matched with 25 individuals randomly selected from the general population and matched with respect to age, gender, and county of residence. On January 1, 1992, the total population in the area was 966,427. The criteria for inclusion in this population-based inception cohort have been described in detail elsewhere.

Pre-scheduled follow-up visits were carried out at 1, 5, 10, and 20 [+/ - 12 months] years after inclusion. All visits included a clinical examination, a structured interview, and laboratory tests. Colonoscopies were performed at all of the visits, unless the patients objected, and otherwise performed as required. Data on all cancer cases, deaths, and causes of death were collected from the Cancer Registry of Norway and from the Norwegian Causes of Death Registry. The Cancer Registry of Norway contains detailed information on each case of cancer. Cancer information comes from several independent sources, thus ensuring a completeness of approximately 98.8%. Moreover, all Norwegian citizens are assigned a unique digital identification number, which makes it possible to link data from several registries and enables highly reliable epidemiological research. All medical doctors in Norway are, by law, obliged to report new and suspected cancers to the Cancer Registry and whether the cancer is first diagnosed by autopsy. With regard to malignancies, all individuals in the study were observed from the date of IBD diagnosis until the first occurrence of cancer, death, or end of follow-up, whichever came first. The International Classification of Diseases [ICD] is the standard diagnostic tool for epidemiology, clinical purposes, and health management. All cancer diagnoses from the Cancer Registry of Norway used in this study were coded according to the ICD-10, and the first occurrence of cancer in each patient and in each of the controls was the diagnosis used in the registration. Our registration did not allow us to distinguish between colonic and rectal cancer, as the diagnoses used included C18 [neoplasma malignum coli] and C19 [neoplasma malignum junctionis rectosigmoidalis], whereas C20 [neoplasma malignum recti] was not applied.

2.1. Definitions and disease classifications

Initially, the patients were classified as having UC, CD, indeterminate colitis [IC], or possible IBD as described previously. Internationally accepted criteria were used for determining the diagnoses and subclassifications.

The patients’ diagnoses were systematically re-evaluated at the pre-scheduled visits at 1, 5, and 10 years after diagnosis. The diagnosis at the 10-year visit was set as the final IBD diagnosis.

Medical treatment was given in accordance with established clinical practice. During the first part of the study period, the patients were given 5-aminosalicylates [5-ASA], glucocorticoids, and thiopurines in a traditional step-up fashion, whereas during the second half of the study, treatment with TNF [tumour necrosis factor]-α inhibitors with or without concomitant immunomodulators was introduced in the treatment of patients with chronic active or severe disease (Table 1).

2.2. Statistical analysis

Data were described with median and range. All IBD patients were age- and gender-matched with individuals selected at random from the general Norwegian population living in the same geographical region [county] [called controls]. Follow-up was defined from the date of IBD diagnosis to the first occurrence of any cancer/specified cancer, death or end of follow-up, whichever came first. Event was defined as the occurrence of any cancer or the first occurrence of a specific cancer. All cancers and specific cancer risks for patients compared with controls were modelled using the Cox proportional model stratified by a matched set. Results are expressed as hazard ratios [HRs] with 95% confidence intervals [CIs]. In addition, for specified cancer groups SIRs [standardized incidence ratios] were computed as a ratio between observed and expected numbers. Expected numbers were derived from gender-stratified tables on cancer incidence in Norway provided by the Cancer Registry of Norway. CIs for the SIRs were constructed using Wilson and Hilferty approximation. Significance level was set to 5%. All analyses were performed using SPSS V. 22.0 for Windows [SPSS; Chicago, IL, USA].

2.3. Ethics

The Regional Committee for Medical Ethics approved the study. The confidentiality of patient identity and records was maintained using the guidelines suggested by the National Health Department.

### Table 1. Patients’ characteristics at diagnosis and cumulative use of immunosuppressive drugs/TNF-α inhibitors during the entire study period.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [females/males]</td>
<td>118/119</td>
<td>252/267</td>
</tr>
<tr>
<td>Treated with AZA</td>
<td>93/193 [50.8%] Missing = 54</td>
<td>48/376 [12.8%] Missing = 143</td>
</tr>
<tr>
<td>Treated with MTX</td>
<td>8/201 [4.0%] Missing = 36</td>
<td>6/447 [1.3%] Missing = 72</td>
</tr>
<tr>
<td>Treated with TNF-α inhibitors</td>
<td>42/176 [23.9%] Missing = 61</td>
<td>12/376 [3.2%] Missing = 143</td>
</tr>
</tbody>
</table>

AZA, azathioprine; MTX, methotrexate; TNF-α inhibitors; tumour necrosis factor-α inhibitors; yr, years.

Treated: patients treated at any time during the study period.
3. Results

Our cohort comprised 756 patients diagnosed with IBD and 18900 age- and gender-matched controls. Demographic data are provided in Table 1. There were no differences in age or gender between the diagnosis groups [data not shown]. The median follow-up time from diagnosis was 21 years [range 1 to 24 years]. Neither the IBD patients nor the controls had been diagnosed with any type of cancer by the start of the study.21,22

A total of 105 individuals in the IBD group [13.9%] developed cancer compared with 1830 in the control group [9.7%]. One subject in the IBD group and three subjects in the control group developed two consecutive cancers. IBD patients had a higher risk of cancer development than their matched controls; however, this increased risk was statistically significant only for UC patients [HR = 1.40, 95% CI 1.08–1.81, p < 0.01 for UC patients; HR = 1.23, 95% CI 0.80–2.03, p = 0.30 for CD patients]. When stratified by gender, our data revealed a higher risk for all cancers only for male UC patients [HR = 1.51, 95% CI 1.08–2.11, p = 0.017]. The cancer risk for female UC patients was elevated compared with that of the controls; however, this increased risk did not reach statistical significance [Table 2]. For CD patients, there was no statistically significant difference in cancer risk between the cases and the controls. The observed and expected numbers of the most common malignancies and SIRs in UC and CD during follow-up are summarized in Tables 3 and 4. Cumulative incidences for cancer development and death for male and female UC and CD patients are shown in Figures 1 and 2. For both genders, cumulative incidence of cancer was higher in IBD patients compared with their controls, also when adjusted for competing risk of death.

3.1. Colorectal cancer

Among female UC patients, 4/252 [1.6%] developed colorectal cancer [CRC], and among male UC patients, the number was 10/267 [3.7%]. In the control group 1.1% of the females and 1.3% of the males developed CRC.

In the CD group, 2/237 patients [0.84%] developed CRC compared with 56/5925 [0.94%] in the control group. The overall risk of males with UC of developing CRC was 2-fold higher compared with that of their controls [HR = 2.41, 95% CI 1.09–3.1, p = 0.029]. For female UC and all CD patients, there were no statistically significant differences in the CRC-specific risk between the cases and their matched controls [Table 2].

3.2. Extraintestinal malignancies

In both UC and CD, the SIR for breast cancer was significantly increased. Moreover, CD patients exhibited an increased SIR for colorectal/lung cancer compared with the controls. The risk of developing malignant melanoma in the UC group was higher than in the control group, but the difference did not reach statistical significance. Generally, very few malignancies in the lymphoid/haematopoietic system were found, and in some diagnostic groups, the CI was so wide that conclusions must be drawn with caution [Tables 2 and 3].

4. Discussion

The present population-based study comprising 756 IBD patients followed for 20 years showed that the UC patients, but not the CD patients, had an increased risk of developing cancer compared with the controls, and male UC patients had an increased risk of developing CRC compared with the controls. The increased risk of having CRC in this UC cohort is in agreement with the findings in a recent meta-analysis of population-based cohort studies in UC patients,23 in which 1.6% of the UC patients were diagnosed with CRC 14 years after diagnosis; SIRs ranged between 1.05 and 3.1. Men with UC had a greater risk than women [SIRs 2.6 vs 1.9]. In our study, 3.7% [10/267] of male and 1.6% [4/252] of female patients with UC developed CRC during the first 20 years after diagnosis.

A Danish study23 did not find an increased overall risk of CRC in UC patients compared with the general population during the first 10 years after diagnosis, which is in accordance with results from the IBSEN study 10 years after UC diagnosis.23 However, a colectomy rate more than twice as high as in other European centres indicates that there may have been a different treatment approach in the Danish study.23,24

Important risk factors for CRC include the duration of the colitis, together with the degree and extent of inflammation, in addition to the presence of primary sclerosing cholangitis and family history of CRC.23 The patients gave information on family cancer history, but such information is lacking in the controls, and, therefore is not analysed further. In our study, we found a high SIR for biliary tract cancers in UC patients compared with the controls but the CI for this risk was wide, making it difficult to draw any conclusions.

In a long-term, nationwide population-based Danish cohort study with 30 years of follow-up, the authors concluded that patients with CD and UC were at increased risk for developing gastrointestinal and extraintestinal malignancies.26 The authors further concluded that the risk of gastrointestinal malignancy has decreased in recent years and that this decrease has occurred without an increase in the overall risk of malignancy. This finding suggests that the benefits of current treatment strategies outweigh the cancer-related risks.

Table 2. Risk of cancer/CRC for IBD patients compared with controls: conditional Cox regression.

<table>
<thead>
<tr>
<th>Variable</th>
<th>UC</th>
<th>CD</th>
<th>p-value</th>
<th>UC</th>
<th>CD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts vs controls</td>
<td>1.40</td>
<td>1.08–1.81</td>
<td>0.010</td>
<td>1.28</td>
<td>0.80–2.03</td>
<td>0.302</td>
</tr>
<tr>
<td>Male pts vs controls</td>
<td>1.51</td>
<td>1.08–2.11</td>
<td>0.017</td>
<td>1.45</td>
<td>0.74–2.85</td>
<td>0.282</td>
</tr>
<tr>
<td>Female pts vs controls</td>
<td>1.28</td>
<td>0.86–1.90</td>
<td>0.227</td>
<td>1.15</td>
<td>0.61–2.18</td>
<td>0.662</td>
</tr>
<tr>
<td>Colorectal cancers [CRCs]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts vs controls</td>
<td>1.90</td>
<td>0.99–3.65</td>
<td>0.054</td>
<td>1.09</td>
<td>0.26–4.54</td>
<td>0.904</td>
</tr>
<tr>
<td>Male pts vs controls</td>
<td>2.41</td>
<td>1.09–5.31</td>
<td>0.029</td>
<td>1.43</td>
<td>0.19–11.05</td>
<td>0.729</td>
</tr>
<tr>
<td>Female pts vs controls</td>
<td>1.27</td>
<td>0.39–4.10</td>
<td>0.689</td>
<td>0.88</td>
<td>0.12–6.34</td>
<td>0.903</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; H, hazard ratio; CI, confidence interval; pts, patients.
The risk of malignancies was also assessed in a large-scale registry study from Finland, where 21,964 patients were followed up for 10.8 years. A higher incidence of cancer among male patients with IBD compared with the background population was found, with a higher SIR for CD than for UC [1.23, 95% CI, 1.09–1.38 vs 1.08, 95% CI 1.02–1.14]. The authors reported a SIR of 1.73 [95% CI 1.30–2.26] in male UC patients and 1.92 [95% CI 1.38–2.59] in female patients for colon cancer, and 1.63 [95% CI 1.18–2.26] and 1.96 [95% CI 1.26–2.91] for male and female patients, respectively, for rectal cancer. In CD, no overall increased risk for developing CRC was observed in either gender, which is in accordance with our findings. Our study included substantially fewer patients but involved a follow-up time that was almost twice as long, as well as including a control group. The study from Finland also showed that UC patients had an excess number of biliary tract cancers [SIR = 7.26, 95% CI 4.37–11.13] and that male patients with UC had an increased risk of Hodgkin lymphomas [SIR = 2.45, 95% CI 1.07–6.78, p = 0.039], whereas UC patients and their controls had equal incidences of these cancer types, but the exact relation to smoking habits was not calculated.

In a meta-analysis of eight population-based cohort studies from 1996 to 2009, comprising approximately 17,000 patients with IBD, the patients were found to have the same overall risk of developing extraintestinal cancers as the background population. In this earlier study, CD patients had an increased risk of cancer of the upper gastrointestinal [GI] tract, lungs, urinary bladder, and skin. UC patients, in contrast, had an increased risk of liver/biliary tract cancers and leukaemia but a decreased risk of pulmonary cancer, which most likely occurred because UC patients smoke less than the background population. Our study confirms the increased risk for cancer of the respiratory tract in patients with CD. Our study also found an increased risk for breast cancer in IBD patients compared with their controls. Breast cancer resistance protein [BCRP] is an example of efflux transporters protecting the enterocytes from toxic compounds. This transporter has been reported to be downregulated in IBD patients, especially those treated with thiopurines, who seem to be at increased risk of developing nonmelanoma skin cancer [NMSC].

In meta-analyses of cohort studies and nationwide studies, IBD patients treated with thiopurines also seem to have a 3–5-fold increased risk of developing lymphoproliferative disorders [LDs] compared with the background population, especially three forms of LD: hepato-splenic T-cell lymphoma, Epstein Barr Virus-related post transplant-like LD, and post-mononucleosis

<table>
<thead>
<tr>
<th>Site [ICD-10]</th>
<th>Observed [n]</th>
<th>Expected [n]</th>
<th>SIR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon/rectum [C18-19]</td>
<td>14</td>
<td>6.36</td>
<td>2.20</td>
<td>1.253.61</td>
<td>0.008</td>
</tr>
<tr>
<td>Biliary tract [C23-24]</td>
<td>2</td>
<td>0.48</td>
<td>4.17</td>
<td>0.7013.77</td>
<td>n.s.</td>
</tr>
<tr>
<td>Trachea/lungs [C33-34]</td>
<td>6</td>
<td>5.52</td>
<td>1.09</td>
<td>0.442.26</td>
<td>n.s.</td>
</tr>
<tr>
<td>Melanoma [C43]</td>
<td>6</td>
<td>3.2</td>
<td>1.86</td>
<td>0.763.90</td>
<td>n.s.</td>
</tr>
<tr>
<td>Basal cell carcinoma [C44]</td>
<td>5</td>
<td>2.2</td>
<td>2.27</td>
<td>0.835.04</td>
<td>n.s.</td>
</tr>
<tr>
<td>Breast [C50]</td>
<td>13</td>
<td>6.48</td>
<td>2.00</td>
<td>1.123.34</td>
<td>0.021</td>
</tr>
<tr>
<td>Prostate [C61]</td>
<td>6</td>
<td>8.56</td>
<td>0.70</td>
<td>0.281.46</td>
<td>n.s.</td>
</tr>
<tr>
<td>Thyroid [C73]</td>
<td>2</td>
<td>0.36</td>
<td>5.56</td>
<td>0.9318.35</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lymphatic leukaemia [C91]</td>
<td>6</td>
<td>1.36</td>
<td>4.41</td>
<td>1.799.18</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases; CI, confidence interval; n.s., not significant.

<table>
<thead>
<tr>
<th>Site [ICD-10]</th>
<th>Observed [n]</th>
<th>Expected [n]</th>
<th>SIR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon/rectum [C18-19]</td>
<td>2</td>
<td>2.24</td>
<td>0.89</td>
<td>0.152.95</td>
<td>n.s.</td>
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<tr>
<td>Biliary tract [C23-24]</td>
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<td>0.04</td>
<td>Cannot be computed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea/lungs [C33-34]</td>
<td>5</td>
<td>1.72</td>
<td>2.91</td>
<td>1.076.78</td>
<td>0.039</td>
</tr>
<tr>
<td>Melanoma [C43]</td>
<td>1</td>
<td>0.8</td>
<td>1.25</td>
<td>0.066.17</td>
<td>n.s.</td>
</tr>
<tr>
<td>Basal cell carcinoma [C44]</td>
<td>1</td>
<td>0.72</td>
<td>1.39</td>
<td>0.076.85</td>
<td>n.s.</td>
</tr>
<tr>
<td>Breast [C50]</td>
<td>6</td>
<td>2.48</td>
<td>2.42</td>
<td>0.985.03</td>
<td>n.s.</td>
</tr>
<tr>
<td>Prostate [C61]</td>
<td>3</td>
<td>2.24</td>
<td>1.34</td>
<td>0.343.65</td>
<td>n.s.</td>
</tr>
<tr>
<td>Thyroid [C73]</td>
<td>1</td>
<td>0.2</td>
<td>5.00</td>
<td>0.2524.66</td>
<td>n.s.</td>
</tr>
<tr>
<td>Lymphatic leukaemia [C91]</td>
<td>0</td>
<td>0.48</td>
<td>Cannot be computed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICD, International Classification of Diseases; CI, confidence interval; n.s., not significant.
lymphoproliferations. The overall risk of developing lymphoma, however, is low, and a lack of association in our study may be present because relatively few patients received immunomodulators.

Interestingly, a pooled analysis of data from 1594 CD patients concluded that the incidence of malignancy with the TNF-α inhibitor adalimumab monotherapy was not greater than that of the general population, but co-administration of immunomodulator therapy was associated with a greater than expected incidence of malignancies other than NMSC [SIR = 3.04, 95% CI 1.08–11.06].

A meta-analysis comprising a total of 17052 IBD patients found that IBD patients overall were not at an increased risk of extraintestinal cancer, but CD patients had an increased risk of cancer in the upper gastrointestinal tract, lungs, urinary bladder, and skin [SIR = 2.87, 1.82, 2.03, and 2.35, respectively]. As shown in the Finnish study, UC patients were at an increased risk of liver/biliary cancer [SIR = 2.85] and were at a reduced risk of lung cancer [SIR = 0.39].

For decades, attention has been given to the possible increased risk for haematological malignancies in patients with IBD, especially those who are treated with immunomodulators and/or TNF-α inhibitors. In our study, six UC patients who had never been treated with immunomodulators/TNF-α inhibitors developed lymphatic leukaemia. None of the CD patients was diagnosed with leukaemia [Tables 2 and 3]. Table 1 shows the cumulative use of immunomodulators/TNF-α inhibitors. The percentage of treated patients is most likely overestimated because most of the patients with missing data are the oldest/dead patients and were often not treated with immunomodulators/TNF-α inhibitors.

Until recently, only anecdotal findings of occurrence of thyroid cancer in UC patients have been published. The Finnish registry study reported SIRs of 2.47 [95% CI 1.18–4.54] and 1.73 [95% CI 1.02–2.72] in male and female UC patients, respectively. In our study, we found two patients with this type of cancer compared with nine in the control group. Since the numbers are small, the interpretation is difficult.

4.1. Strengths and limitations of the present study

Major strengths of the present study include the longitudinal, prospective approach in a well-defined population-based cohort and the accurate detection of cases of malignancies through the national registries. The limited inclusion period and the fact that dedicated specialists and hospitals were responsible for the diagnostic procedures
are factors that contribute to a uniform diagnostic and therapeutic approach. People in Norway do not tend to move house very often, and it is therefore easier to perform prospective long-term studies. All patients had the same duration of follow-up in the identical time period, and each patient was age- and gender-matched with controls from a national registry with very high completeness and quality.

All citizens in Norway are assigned a unique ID number, which enables easy and accurate identification and linkage of medical and death certificate records. There is no reason to assume that inclusion in this study influenced the classification of cancer in the IBD group compared with the background population.

There were some limitations of the study. Even with the high number of patients included in this prospective cohort study, the occurrence of cancers was low which implies a limited statistical power. At diagnosis, the median age of the UC and CD patients was 38 and 29 years, respectively, indicating that the patients were relatively young, even 20 years later. Hence, it is to be expected that an extension of the observation period would reveal increased numbers of IBD-related cancers within this group. The levels of education and socioeconomic conditions were not taken into consideration, mainly due to a lack of data. These differences are not marked in Norway. Because the cohort was regularly examined and the control group was not, the probability of being diagnosed with cancer at an earlier stage may have been higher among the patients than among the controls.

5. Conclusion

This population-based inception cohort study revealed that patients with a 20-year history of IBD had an increased risk of cancer compared with matched controls from the general population. Most of the excess risk was derived from an increased risk for colorectal cancers in male UC patients. This study also reveals a statistically significant increase in risk for lymphatic leukaemia and breast cancer in UC patients and for trachea/lung cancer and breast cancer in CD patients, compared with the rates seen in the general population, but the numbers here are small.

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Conflict of Interest

The authors have nothing to disclose.

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Author Contributions

ØH: acquisition of data, analysis and interpretation of data, drafting of the manuscript, revision of the manuscript. MLH: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MH and ICS: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MCS: statistical analysis, critical revision of the manuscript for important intellectual content. BAM: study concept and design, analysis and interpretation of data, revision of the manuscript for important intellectual content, obtained funding, study supervision.

References